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Phototransduction in *Drosophila*

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The *Drosophila* visual transduction is the fastest known G protein-coupled signaling cascade and has been served as a model for understanding the molecular mechanisms of other G protein-coupled signaling cascades. Numbers of components in visual transduction machinery have been identified. Based on the functional characterization of these genes, a model for *Drosophila* phototransduction has been outlined, including rhodopsin activation, phosphoinoside signaling, and the opening of TRP and TRPL channels. Recently, the characterization of mutants, showing slow termination, revealed the physiological significance and the mechanism of rapid termination of light response.

GPCR signaling, visual transduction, rhodopsin, TRP channels, *Drosophila*

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1 Overview and relationship of *Drosophila* to mammalian phototransduction

Drosophila vision is the first sensory system that has been detailed studied using genetic analyses in any animal [1]. Now we know that *Drosophila* vision is the fastest known G protein-coupled signaling cascade, which is activated in less than 20 milliseconds [2]. In *Drosophila*, visual transduction is initiated by the photon-induced isomerization of chromophore in rhodopsin, and subsequently activates the heterotrimeric G protein. The effector of the heterotrimeric GTP-binding protein is phospholipase Cβ (PLC) [3], which leads to the opening of the TRP and TRPL cation channels (Figure 1) [4–7]. In vertebrate rods and cones, visual transduction is also initiated by the activation of rhodopsins and subsequent interaction with heterotrimeric G proteins (transducin). However, in rods and cones, the downstream effector of transducin is a cyclic guanosine monophosphate (cGMP) phosphodiesterase, which leads to the reduction of cGMP levels, and subsequently closes the cGMP-gated channels [8]. Thus, the consequences of light stimulation on the channels are opposite, opening the channels in fly photoreceptors and closing the channels in rods and cones.

Although the visual transduction cascades are different between fly photoreceptors and mammal rods/cones, mammalian ipRGCs phototransduction cascades show the similarity with fly visual transduction. ipRGCs are the small subset of intrinsically photosensitive retinal ganglion cells, which function in photoentrainment of circadian rhythm and in light-induced papillary constriction [9]. In the ipRGCs, the cascade is initiated through melanopsin, which shows

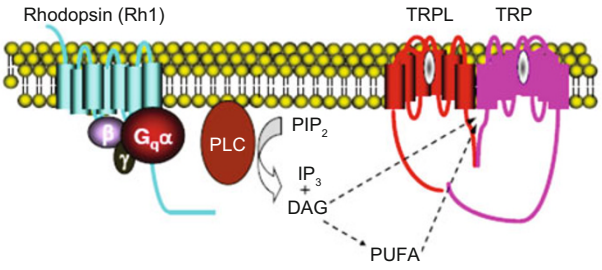

Figure 1 Model of the *Drosophila* phototransduction cascade.

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higher similarities in sequence and biophysical properties to fly rhodopsins than the light receptors in rods and cones [10–16]. Some studies have demonstrated that ipRGC cascade functions through the activation of PLC and the opening of channels, which displays the features of TRP channels [10,17,18].

2 The anatomy of *Drosophila* visual system

Drosophila visual system consists of the retina and the optic lobe known as the lamina, the medulla, the lobula, and the lobula plate (Figure 2A). *Drosophila* compound eye comprises approximately 750 unit eyes, called 'ommatidia' (Figure 2B and C). One ommatidium contains 20 cells, eight of which are photoreceptor cells (R cells, R1-R8) (Figure 2C) [19]. The main cells surrounding the photoreceptor cells are secondary pigment cells. Peripheral photoreceptors (R1–6) arrange as a hexagon and extend the retina, while central photoreceptors (R7 and R8) reside in the centre and occupy the distal and proximal regions of the ommatidia, respectively (Figure 2A). R1-R6 expresses major Rhodopsin (Rh1), which is sensitive to a broad spectrum of light with a maximum sensitivity in 486 nm [20,21]. Peripheral photoreceptors function as the rod cells in vertebrate, and mediate motion detection. R7s express about 30% and 70% of the rhodopsin Rh3 and Rh4 respectively, which are sensitive to ultraviolet light. While R8s express the blue light-sensitive Rh5 and green light-sensitive Rh6 opsin, respectively, with the same relative proportions as R7 photoreceptors in a seemingly random distribution pattern [22–25]. R7 and R8 neurons are thought of the equal function as vertebrate cone cells, and are specialized for color vision.

R-cell neuron axons from a single ommatidium form a bundle to innervate the lamina (R1-R6) and the medulla (R7 and R8) optic ganglia (Figure 2A). R1-R6 axons terminate in the lamina and connect with the lamina neurons to form synaptic units called 'cartridges' (Figure 2D). Each cartridge contains R1-R6 input terminal from six separate ommatidia, five lamina neurons (L1-L5), and several other cell types (Figure 2E) [26]. The projection pattern of the R1–R6 axons mirrors the arrangement of their rhabdomeres in the ommatidium. This kind of organization facilitates to pool the visual input from the R1–R6 neurons from six separate ommatidia.

The membrane of each photoreceptor cell forms a stack microvillar structure, called rhabdomere, which is the functional equivalent of the rod and cone outer segment in mammals (Figure 2C). Each R1-6 neuron contains about 50000 microvilli, whereas each R7/8 neuron contains about 17000 microvilli. Each microvilli provides a massive plasma membrane surface to anchor a high concentration of rhodopsin and the proteins that function in phototransduction.

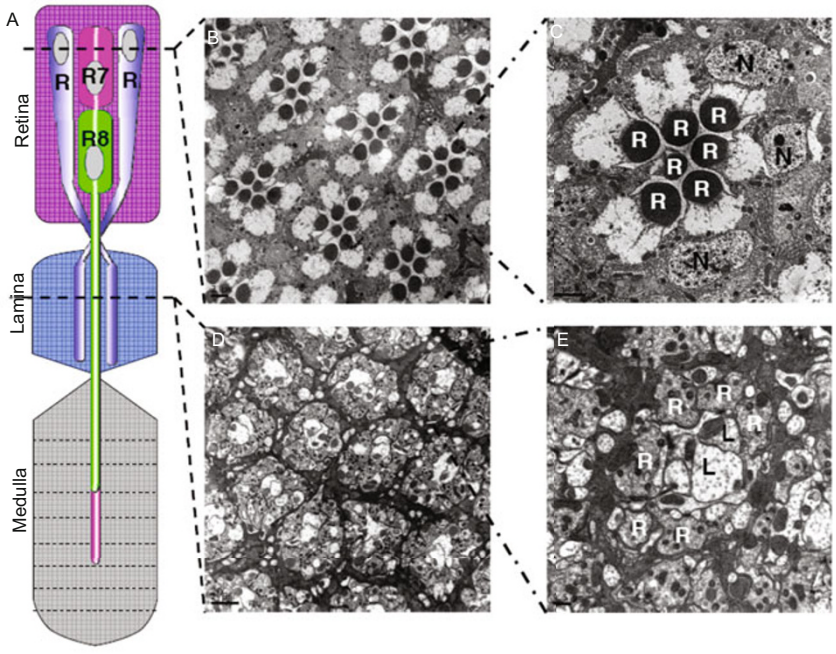

Figure 2 The anatomy of the fly visual system.

(A) Connection patterns of the photoreceptor neurons. Each ommatidium contains eight photoreceptor neurons (R1–R8). R-cell axons from a single ommatidium form a bundle to innervate the lamina (R1-R6) and the medulla (R7 and R8) optic ganglia. Single ommatidium is shown. R, photoreceptor cells 1–6; R7, photoreceptor cell 7; R8, photoreceptor cell 8. (B) EM image of eye cross section through the distal regions of the ommatidia. The eye comprises about 750 ommatidia, each of which contains eight photoreceptor neurons termed R1–R8. (C) Enlarged EM image from B. Seven photoreceptor cells are present N. necleus. (D) EM image of cross section through the lamina. R1-R6 axons terminate in the lamina and connect with the lamina neurons to form synaptic units, cartridges. (E) Enlarged EM image from D. Each cartridge contains R1-R6 input terminal from six separate ommatidia, five lamina neurons (L1-L5). Two lamina neurons are labeled R, R-cell axons; L, Lamina neuron.

3 Genetic approaches of *Drosophila* phototransduction

Early genetic screens for the mutations affecting visual response were performed on behavioral assays, such as phototaxis or optomotor response in adult flies [27–29]. Retinal degeneration screens also isolated some mutations that show defective phototransduction [28,30,31]. In the late of 1960s, light-evoked electrophysiological responses of the eye (electroretinogram, ERG) were used in the studies of phototransduction [32,33]. ERGs are extracellular recordings, which measure the summed responses of the compound eye to light [34]. Later, ERG based chemical mutagenesis screens turned highly effective and productive in the isolation of mutants that display defective phototransduction. The ERG assays not only identified all the mutants isolated in behavioral screens but also isolated many additional mutants that were not identified by behavioral screens [35]. From the late 1960s to the late 1970s, more than 200 mutants that display defective ERG response were isolated from approximately 10^5 flies.

For ERG recording, live flies are immobilized and two glass microelectrodes filled with ringer's solution are put separately on the eye surface and the thorax (as reference). High intensity light pulses (4000 lux) are used to stimulate the eye of fly. Once the light turns on, the phototransduction cascade is activated, TRP and TRPL channels are opened, the photoreceptor neurons depolarize in 20 milliseconds. The photoreceptor neurons maintain in the depolarization status during the light stimulation. When the light turns off, the phototransduction cascade is deactivated, TRP and TRPL channels are closed, and the photoreceptor neurons re-polarize in 100 milliseconds [34,36,37]. There are several primary features of the ERG response, the activation speed and amplitude that reflects the activation of phototransduction cascade, the maintenance of depolarization status, the termination speed that results from the deactivation of phototransduction cascade, and the on- and off- transients, which occur due to the feedback of postsynaptic activity to the photoreceptor cells in the lamina. We summarized the mutants display abnormal ERG responses with different features (Table 1).

Although the forward genetic screens identified many genes required for phototransduction (Table 1), mutagenesis was not carried out to saturation. Therefore, using reverse genetic approaches, several genes, encoding components of the phototransduction machinery, have been identified and well studied. For example, combined reverse genetics and western blotting analysis, *Drosophila arrestin* mutants were successfully isolated [38]. Some mutants were isolated in the related studies. One mutant was first isolated for the defects in following of visual cues in courtship. Finally, it was confirmed that this allele is a spontaneous mutant of the *transient receptor potential* (*trp*) gene, which encodes a light-activated channel subunit [6].

It is possible that some of the eye-enriched genes might function in the phototransduction pathway, because the identified components of phototransduction machinery are usually highly expressed in the eye. Based on this hypothesis, nearly 100 uncharacterized eye-enriched genes were identified in the DNA microarray analysis [39]. Two eye-enriched genes have been characterized to function in the visual response [39–41].

4 Activation of the phototransduction cascade

Phototransduction cascade is initiated by the activation of rhodopsin, which is comprised of a seven transmembrane protein, opsin, and a chromophore. The chromophore is covalently linked to a lysine residue in the seventh transmembrane domain through a Schiff base. In vertebrates the chromophore is 11-*cis* retinal, while in *Drosophila* it is 11-*cis* 3-hydroxyretinal [42]. Photon absorption leads to the photoisomerization of chromophore, and results in the conformational change of opsin, forming the activated metarhodopsin. In vertebrates, *all-trans* retinal subsequently dissociates from metarhodopsin and re-isomerizes through a lengthy enzymatic pathway. In rods, it takes approximately 30 min for retinal to be re-isomerizes and absorbed by rhodopsin. In contrast, *Drosophila* metarhodopsin is usually thermostable, and retinal does not dissociate from metarhodopsin and can be directly re-isomerized back by absorption of 580 nm light [43].

Metarhodopsin in turn activates heterotrimeric G proteins by shifting α-subunit from an inactive GDP-bound form to active GTP-bound form [43–45]. Activated G protein α-subunit then dissociates from the receptor and opens the cascades. In vertebrates, the downstream effector for the G protein is a phosphodiesterase, which hydrolyzes 3′-5′ cyclic guanosine monophosphate (cGMP) to 5′ GMP, and leads to the closure of cGMP-gated ion channels to terminate the Na^+ and Ca^{2+} influx [46,47]. In contrast, the effector for the *drosophila* heterotrimeric G protein is PLC, which catalyzes phosphatidylinositol-4,5-bisphosphate (PIP_2) to form inositol-1,3,5-trisphosphate (IP_3) and diacylglycerol (DAG) [3,48–50]. Activation of PLC results in the opening of cation influx channels and leads to Na^+ and Ca^{2+} influx [2,6].

5 Deactivation of the phototransduction cascade

In the first decade, the study of phototransduction focused on the activation of visual signaling by isolating defective mutants and by identifying the components. Recently, people try to reveal the mechanisms of deactivation in visual response, because timely deactivation is required for the receiving of subsequent stimulation and preventing toxicity

induced by excessive Ca^{2+} influx [51].

The most important step in phototransduction termination is the deactivation of metarhodopsin. In this step, Arrestins plays a critical role by displacing Gq α subunit to bind with rhodoposin [38,52,53]. *Drosophila* photoreceptor cells contain two Arrestins, Arrestin1 and Arrestin2 (Arr 1 and Arr 2) [54–56]. Arr2, the major isoform of Arrestins, plays the predominant roles in the deactivation of rhodopsin[38], while Arr1 mediates light-dependent rhodopsin endocytosis [52]. Different from other GPCR signaling pathway, the phosphorylation of fly rhodopsin is not required for its deactivation [57], but is essential for its endocytosis [52]. However, the dephosphorylation of rhodopsin is critical for receptor deactivation [58].

A novel mechanism for rhodopsin deactivation, which involves a CaM binding transcription factor, dCAMTA, and its transcriptional target, *dFbx14*, has been demonstrated [36]. The role of FBXL4 in regulating the photoresponse termination remains to be investigated. It is possible that there are some additional mechanisms that function in rhodopisn deactivation, as photo response can still be terminated in *dcamta;arr2* double mutant flies [36].

G protein is deactivated by promoting the hydrolysis of GTP to GDP. As a signaling switch, PLC also deactivates G protein through its C-terminal region in stimulating the intrinsic GTPase activity of Gq α [59, 60].

A couple of molecules participate in TRP deactivation. INAC has been shown to play critical roles in deactivating TRP channels [61]. INAC is one member of the PKC family of serine/threonine protein kinases [62,63], which is activated by Ca^{2+} and DAG [64]. Using phosphorylation assays in isolated signaling complexes, TRP was identified to undergo Ca^{2+}-dependent phosphorylation modification [61]. CaM is likely to be another regulator in the deactivation of TRP and TRPL channels. *In vitro* studies showed that both TRP and TRPL bind to CaM through their C-terminals [5,65,66]. *In vivo* studies demonstrated that the CaM binding sites of TRPL are critical for rapid termination and *cam* mutant shows slow termination defects [67]. Additional, Ca^{2+} also plays a critical role in the deactivation of light response [68, 69]. In the whole-cell recordings of photoreceptor cells, termination speed depends on the Ca^{2+} [69–71].

Based on these studies, several negative feedback regulation loops exist in the deactivation of visual response. Ca^{2+}/CaM/INAC/TRP pathway serves as a rapid negative feedback regulation and Ca^{2+}/CaM/dCAMTA/FBXL4 pathway acts as a slow negative feedback regulation. Other deactivation mechanisms need to be further investigated.

Table 1 Transduction mutants and phenotype

Gene	Molecular function	Alleles	Mutagen	ERG phenotype	References
arr1	Minor arrestin, metarhodopsin binding	$arr1^1$	Insertion in the 2nd intron		[72]
		$arr1^2$	C^{154}→S		[72]
		$arr1^3$	V^{52}→D	PDA defect	[58]
arr2	Major arrestin	$arr2^5$	Y^{20}→stop	Slow termination; ERG amplitude reduced	[73, 74]
		$arr2^3$	V^{52}→D	Slow termination;	[38]
calx	Na^+/Ca^{2+} exchanger	$Calx^A$	T822→I	no PDA, inactivation of light response	[75]
cam	Calmodulin,	cam^{352}	Deletion the promoter	Slow termination	[76]
camta	Cam binding transcription activator	$camta^{tes\text{-}1}$	Q398→stop	Slow termination	[36]
		$camta^{tes\text{-}2}$	S577→R;L1420→stop	Slow termination	[36]
cdsA	CDP diglyceride synthetase	$CdsA^1$	P-element activity	Reduction in light sensitivity;	[77]
Calnexin	rhodopsin chaperone			No PDA	[78]
cry	Cryptochrome	cry^b	D410→N	very low light sensitivity	[79]
Gα49B	α subunit of G protein	$Gα49B^1$ $Gαq^1$	Deletion of 154-156 aa	~1000-fold reduction in sensitivity to light; slow termination; increased activation latency	[50, 80]
Gβ76C	β subunit of G protein	$Gβe^2$	G^{288}→E	Reduced light sensitivity; slow termination	[81]
		$Gβe^1$	C^{293}→Y	Reducted light sensitivity; slow activation; slow termination	[82]
Gγ30A	γ subunit of G protein	$Gγ30A^{C69}$	C69→G Constructive mutant	Low light sensitivity	[83]
Gprk1	Rhodopsin kinase	$Gprk1^{hs.PL}$	An Hsp70 promoter drives expression of Gprk1.	Small amplitude	[84]
inaC	Protein kinase C (PKC)	$inaC^1$	V^{201}→D	Slow termination; defective PDA	[2]
		$inaC^2$ $inaC^{209}$	W^{93}→stop	Slow termination; slowly decaying receptor potential during the light pulse in ERGs;	[85]
		$inaC^5$	W^{139}→stop	Slow termination	[85]
inaD	Scaffold protein; 5 PDZ domains	$InaD^1$ $InaD^{P215}$	M^{442}→K	Defective PDA; decay following the peak response in ERG	[86]
		$inaD^{T1}$ $inaD^1$	R^{270}→stop	ERGs: responding only at the highest light intensities smaller amplitude;	[87, 88]
		$inaD^{T2}$	G^{605}→E	ERGs: latency, activation and deactivation are all significantly slower; smaller amplitude	[88, 89]

(*To be continued on the next page*)

(*Continued*)

Gene	Molecular function	Alleles	Mutagen	ERG phenotype	References
inaF	Putative regulator of TRP	$inaF^{P106x}$	Delete the ORF and 3′-UTR and 5′-UTR	reduction in light response and longer response latency in intracellular recordings	[90]
laza	PA phosphatase	$laza^{GE}$	P-element activity	Small amplitude	[41]
		$laza^{1}$	Delete *laza* (-317 to +1381)	Small amplitude; Slow termination	[41]
		$laza^{2}$	Delete *laza* (-309 to +913)	Small amplitude; Slow termination	[41]
ninaA	Cyclophilin	$ninaA^{1}$ $ninaA^{P228}$	W^{208}→stop	At restrictive temperature, defective PDA	[91]
		$ninaA^{2}$ $ninaA^{P269}$	Q^{87}→stop	Defective PDA	[92]
ninaB	Retinal isomerase	$ninaB^{1}$ $ninaB^{P315}$	E^{280}→K;M^{471}→L;E^{477}→A	no PDA	[92]
ninaC	Protein kinase	$ninaC^{5}$ $ninaC^{P235}$		slow termination; defective off-transient	[93, 94]
		$ninaC^{\Delta 174}$	T-G transversion in the second base of the tenth intron	slow termination; defective off-transient	[95]
ninaD	Scavenger receptor	$ninaD^{2}$ $ninaD^{P246}$		No PDA	[92, 96]
ninaE	Major rhodopsin	$ninaE^{7}$ $ninaE^{P332}$	G^{128}→R	No PDA; reduction in sensitivity to light; no on-transient;	[97]
		$ninaE^{8}$ $ninaE^{P334}$	T^{283}→M;W^{289}→R;C^{297}→S	No PDA; very small ERG response; no on-/off transient;	[96]
		$ninaE^{17}$ $ninaE^{117}$	1.6 kb deletion of the 5′ flanking and 5′ coding regions	No PDA; very small ERG response; no on-/off-transient	[98, 99]
ninaG	Oxidoreductase	$ninaG^{P330}$	Q71→stop	No PDA	[100]
norpA	Phospholipase C (PLC)	$norpA^{36}$ $norpA^{P24}$ $norpA^{P29}$	deletion (2710–2737); substitution of 24 amino acid residues, followed by a premature termination codon	No ERG	[101]
		$norpA^{7}$ $norpA^{EE5}$		Very small response	[30,102]
		$norpA^{31}$ $norpA^{H52}$	S^{551}→Y	At restrictive temperature, no photoreceptor potential.	[103]
ort	Histamine-gated Cl^- channel	ort^{1}	Deletion of intron 2 (110bp) and 459 nucleotides of exons 2 and 3	No PDA, light coincident response is reduced in amplitude, transient components missing.	[97,104]
		ort^{4}		Slow termination kinetics after a long pulse; a faster repolarization after a short pulse;	[105]
pinta	Retinoid binding	$pinta^{1}$	F90→stop	No PDA	[96]
pis	CDP-diacylglycerol-inositol 3-phosphatidyltransferase	pis^{1}	replacement of a part of the Pis gene with w	Inactivation during light response	[106]
Pld	Phospholipase D (PLD)	$Pld^{null.3'}$	Lack the promoter, exon 1 and most of exon 2 and contain a premature STOP codon within exon 5.	Low (~1.9%) light sensitivity	[102]
		$Pld^{null.5'}$	lacks most of exon 9, K1002→STOP	Low (~1.9%) light sensitivity	[102]
Pph13	Homeobox	$Pph13^{hazy}$	W^{58}→stop	Absence of on- and off-transients	[107]
rdgA	DAG kinase	$rdgA^{1}$ $rdgA^{BS12}$	Q^{1153}→stop	Only minimal ERGs in extremely newly emerged flies	[108]
		$rdgA^{2}$ $rdgA^{KO14}$	G^{869}→D	ERG of 7 day old flies shows reduced receptor potentials	[30]
rdgB	PI transfer protein	$rdgB^{2}$		Very small ERG response of 1-day-old flies	[109]
		$rdgB^{9}$ $rdgB^{KS222}$	Q^{147}→stop	Small ERG response without on/off-transient;	[30]
rdgC	Rhodopsin phosphatase	$rdgC^{306}$		slow termination	[74, 84]
repo	RNA polymerase II transcription factor	$repo^{1}$	P-element activity	Homozygotes exhibit an age-dependent reverse polarity ERG recording.	[110]
rtp	Retinophilin	rtp^{1}	Delete the translation initiation codon and the following two methionine codons	reduced PDA	[111]
santa-maria	Scavenger receptor	$santa\text{-}maria^{1}$	G^{217}→D	No PDA	[112]
stmA	Possible lipase in PIP2 pathway	$stmA^{1}$ rbo^{ts}	G^{487}→D	At 37°C, the ERG is completely eliminated in these flies.	[113]
t	β-Alanyl-histamine hydrolase	t^{1}	R^{127}→P	ERG abnormal	[114]
		t^{8}		ERG abnormal	[115]
trp	Ca^{2+} channel	trp^{2} trp^{301}		Transient potential; reduction in light response	[116, 117]
		trp^{9} trp^{343}		Transient potential, reduction in light response and longer response latency	[116, 118]
		trp^{P365}	Pro^{500}→Thr;His^{531}→Asn Phe^{550}→Ile;Ser^{867}→Phe	Very small ERG response, but not transient	[119]
trpl	Ca^{2+} channel	$trpl^{302}$	Q^{302}→stop	The receptor potential is smaller.	[116]

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